Annals of Oncology Advance Access published March 27, 2015

review

Annals of Oncology 00: 1–7, 2015
doi:10.1093/annonc/mdv106

Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (*D*efinition for the *A*ssessment of *T*ime-to-event *E*ndpoints in *CAN*cer trials)†

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Received 30 January 2014; revised 28 January 2015 and 16 February 2015; accepted 16 February 2015

Background: Using surrogate end points for overall survival, such as disease-free survival, is increasingly common in randomized controlled trials. However, the definitions of several of these time-to-event (TTE) end points are imprecisely which limits interpretation and cross-trial comparisons. The estimation of treatment effects may be directly affected by the definitions of end points. The DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer

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†This work was presented as a poster communication at the following meetings: ASCO (Chicago, June 2013), ECCO/ESMO (Amsterdam, September 2013), and SABCS (San Antonio Breast Cancer Symposium, San Antonio, December 2013).

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trials) aims to provide recommendations for definitions of TTE end points. We report guidelines for randomized cancer clinical trials (RCTs) in breast cancer.

Patients and methods: A literature review was carried out to identify TTE end points (primary or secondary) reported in publications of randomized trials or guidelines. An international multidisciplinary panel of experts proposed recommendations for the definitions of these end points based on a validated consensus method that formalize the degree of agreement among experts.

Results: Recommended guidelines for the definitions of TTE end points commonly used in RCTs for breast cancer are provided for non-metastatic and metastatic settings.

Conclusion: The use of standardized definitions should facilitate comparisons of trial results and improve the quality of trial design and reporting. These guidelines could be of particular interest to those involved in the design, conducting, reporting, or assessment of RCT.

Key words: guidelines, randomized, controlled trial, time-to-event end point, efficacy measure, breast cancer

introduction

In randomized cancer clinical trials (RCTs), the validated and most objectively defined evaluation criterion is overall survival (OS), characterized as the time from randomization to patients' death (all causes). The development of new cytotoxic agents, the current context of strategic trials, and the multiplication of lines of treatment, especially in breast cancer, have significantly reduced mortality in certain contexts. This therapeutic progress has resulted in the need for surrogate end points and/or intermediate end points for OS. Such end points are being increasingly used in cancer RCTs. Thus, disease-free survival (DFS) and progression-free survival (PFS) have been used as surrogate end points of OS in non-metastatic and metastatic settings, respectively. These surrogate end points are gradually replacing OS [1] and their development has been strongly influenced by the need to reduce the number of patients taking part in RCTs, as well as the duration and, ultimately, the cost of RCTs.

As recommended by the International Conference on Harmonisation (ICH) guidelines [2] and by the CONSORT statement [3], each time-to-event (TTE) end point should be precisely defined. It implies specifying the date of origin, the list of events to be considered, such as failures, and the censoring process. However, despite their extensive use, most TTE end points are often poorly defined, and when a definition is provided, it varies from one publication to another as underlined by a recent study published in the *Journal of Clinical Oncology* [4] and by the Food and Drug Administration (FDA) [5]. As an example, in a review of RCT in oncology, Mathoulin-Pélissier et al. [4] showed that a clear definition of survival end points was reported for only 52% of cancer RCTs published in major journals. The heterogeneity of definitions for TTE end points was recently highlighted by the international community, as demonstrated by all the publications recommending the definition of specific criteria and/or the preferred use of certain criteria in specific localizations such as for colorectal cancer in the adjuvant setting [6], hepatocellular carcinoma [7], lymphoma [8], or breast cancer [9]. However, most of these recommendations were usually based on experts' opinions, without formal international consensus process, and without representation of academic groups in the selected panels of experts, facts that may explain why they have not been widely accepted in current practice.

It is important to distinguish the process of selecting a relevant end point from the action of defining this same end point. The selection of TTE end points to assess a therapeutic strategy depends on the characteristics of a given trial including settings (adjuvant versus metastatic) and treatments (systemic, local, or any combination thereof). As such, the choice of the end points is trial-specific. Once the end point is identified, it then has to be appropriately defined, ideally using a standardized definition to enable future comparisons.

Using a formal consensus process, we set up the international DATECAN initiative (*D*efinition for the *A*ssessment of *T*ime-to-event *E*ndpoints in *CAN*cer trials) [10], which aimed to obtain standardized consensus definitions of TTE end points for multiple cancer sites: breast; sarcomas/gastro intestinal stromal tumors (GISTs); pancreas; stomach/esophagus; head and neck; colon/rectum; kidney/bladder; and lung cancers. Here, we report guidelines for the definition of TTE end points used in breast cancer RCT as primary or secondary end points.

methods

The DATECAN project was launched in 2010 regarding three cancer sites: breast, sarcoma/GIST, and pancreatic cancer. The coordinating committee (CC) for the breast cancer part of the project included two experts (SG-B and TSD-Y).

consensus process

A formal consensus method was used to develop these guidelines [11, 12]. Its purpose was to formalize the degree of agreement among experts using iterative ratings with feedbacks to identify and select points on which there was either disagreement or uncertainty. The guidelines were subsequently based on the agreement scores. The formal consensus method involved the following steps (Figure 1): (i) the assessment of the evidence with regard to the research question; (ii) the elaboration followed by the pre-testing of the questionnaire before collecting experts' opinions; (iii) the scoring of the questionnaires; (iv) the analysis of the experts' opinions and the drafting of the final report; (v) the peer-review step; and (vi) the diffusion of the recommendations. An overview of these steps is provided in supplementary Material S1, available at *Annals of Oncology* online. A full description of the methodology of the consensus process has been published in a former study [10].

literature review

We conducted literature reviews to assess the development of guidelines for TTE end points and listed TTE end points

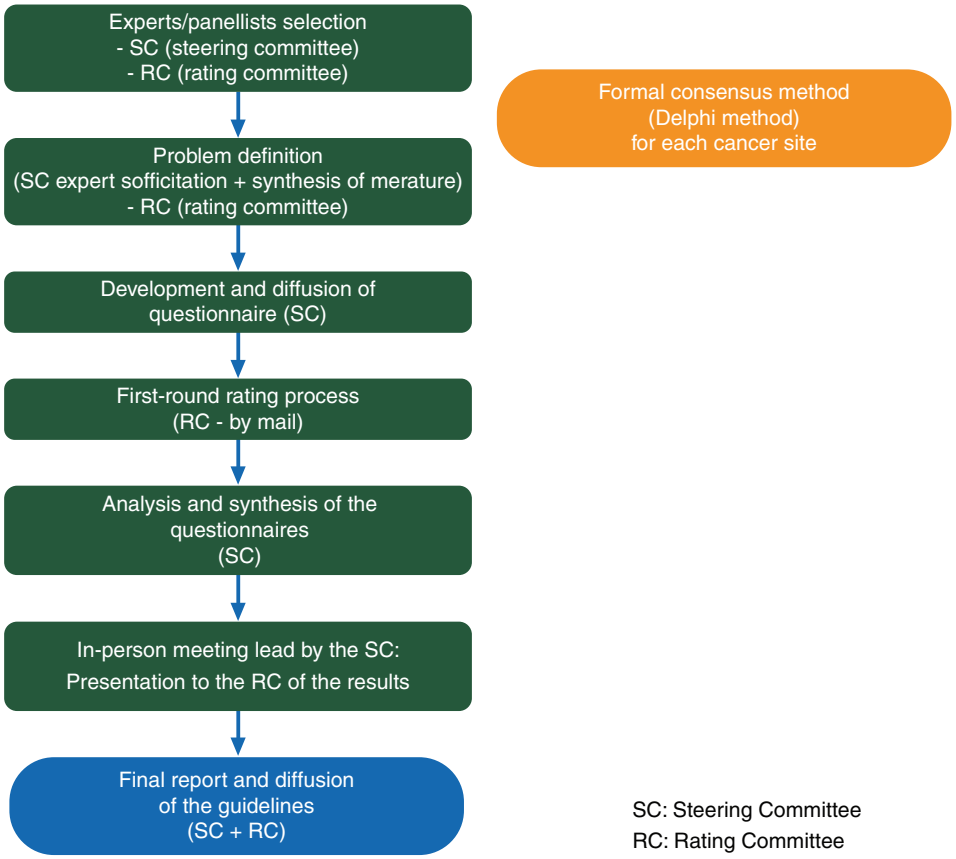

Figure 1. A modified Delphi method used in the DATECAN initiative to reach consensus for time-to-event end points in randomized, controlled trials for breast cancer.

commonly reported in an RCT, either as primary or secondary end points. The research algorithms used are available in supplementary Material S2, available at *Annals of Oncology* online.

questionnaires

All experts had to fill in a first questionnaire: they all received the same questionnaire to score each TTE end point on a scale of 1 (*totally disagree*) to 9 (*totally agree*), according to whether various clinical events should be regarded as events in the definition of TTE outcomes. After the first round, the second questionnaire was personalized for each expert (supplementary Material S3, available at *Annals of Oncology* online).

Items for which a strong consensus had been reached after the first questionnaire were highlighted. For items with no consensus found, the distributions of scores obtained during the first round were summarized (minimum, maximum, and median scores) and the initial score of the RC expert was indicated. In second questionnaire, experts were asked to re-score the items for which no consensus had been reached in the first round.

results

selection of TTE end points to be defined and clinical events of interest

Eleven end points were selected from the literature, according to the trial setting (non-metastatic [9] or metastatic [2]) and for which no consensus methodology in adjuvant settings had been described [9]. Clinical events, which could be included in the definition of these end points, were identified (Table 1).

experts for the scoring process

The CC drafted a list of 50 experts from European countries to include in the rating committee, meeting twice. Because of an over-selection of French experts at the first selection step, we opened the scoring process to additional experts from other Europeans countries. Of the 35 experts who filled-in the first questionnaire, 31 (89%) also answered the second questionnaire. They were specialists in medical oncology ($n = 14$; 45%), radiation oncology ($n = 4$; 13%), surgery ($n = 4$; 13%), pathology ($n = 4$; 13%), and methodology/biostatistics ($n = 5$; 16%; supplementary Material S4, available at *Annals of Oncology* online). These experts worked in institutions from many countries, such as France, Belgium, UK, the Netherlands, Portugal, Italy, Germany, Denmark, Slovenia, and Switzerland. They belonged to various cooperative groups including breast cancer groups from the EORTC (European Organization for Research and Treatment of Cancer), UNICANCER (French Group of Comprehensive Cancer Centers), the American Society for Radiation Oncology (ASTRO), the French Society for Radiation Oncology (SFRO), and from the National Cancer Research Institute Breast Cancer Group of the United Kingdom (NCRI), the Dutch Breast Cancer Trialists' Group (BOOG), and the Italian Breast Cancer Group.

Table 1. Time-to-event end points considered for the elaboration of definitions and clinical events that could possibly be included in their definitions

Time-to-event end points
Breast cancer-specific survival (BCSS)
Invasive disease-free survival (iDFS)[a]
Distant disease-free survival (D-DFS)
Distant relapse-free survival (D-RFS)
Relapse-free survival (RFS)
Locoregional relapse-free survival (L-RFS)
Recurrence-free interval (RFi)
Breast cancer-free interval (BCFi)
Distant recurrence-free interval (D-RFi)
Progression-free survival (PFS)
Time-to-progression (TTP)
Clinical events
Invasive ipsilateral breast tumor recurrence/progression
Local invasive recurrence/progression
Regional invasive recurrence/progression (M+: Regional progression)
Invasive contralateral breast cancer
Appearance/occurrence of metastases/distant recurrence
Second primary invasive cancer (non-breast cancer)
Death from breast cancer
Death from non-breast cancer cause
Death related to protocol treatment
Death from any cause
Death from unknown cause
Ipsilateral DCIS
Contralateral DCIS
Lost to follow-up

[a]Initially named 'disease-free survival' and renamed by the experts.

consensus rates after the two rounds of rating

The consensus process was constituted of two rounds of rating (first round: January 2011 to January 2012; second round: February 2012 to May 2012) and one face-to-face meeting (3 June 2012, Chicago). During the first round, experts were asked to rate a total of 150 events pertaining to 11 TTE end points. At that step, a strong consensus was reached for 6 (4%) of the events for two end points. After the second round, a strong consensus was reached for 60 events (42%), and strong or relative consensus was reached for 80 events (56%). After the two steps of rating process, no consensus was reached for 70 events covering the 11 end points. Those events were thus discussed at the face-to-face meeting.

face-to-face meeting

Before discussing each event on an individual basis and with the aim of harmonization, experts present at the meeting first took a number of decisions. The aim of this preliminary discussion was triple: to select the items that would be discussed, to maintain the consensus process even though not all experts attended the meeting and some experts were therefore unavailable for discussion, and to decide the procedure to adopt in case of an absence of consensus.

standardized definitions of the TTE end points

Table 2 lists the events that need to be included in the definition of each TTE end point following the consensus process, depending on the disease setting (non-metastatic, metastatic, or both settings).

Among the 11 end points initially listed, one was considered ambiguous (DFS) and renamed by the experts as invasive DFS, iDFS.

Two definitions for two different end points were identical: distant DFS (D-DFS) and distant relapse-free survival (D-RFS).

The reference date was usually the date of randomization, but it could also be the date of diagnosis or treatment initiation, depending on the study. End points were defined according to the setting. Nine end points were specifically defined for the non-metastatic setting: breast cancer-specific survival (BCSS), iDFS, D-DFS, D-RFS, RFS, locoregional RFS (L-RFS), recurrence-free interval (RFi), breast cancer-free interval (BCFi), and distant recurrence-free interval (D-RFi). Two end points were designed for the metastatic setting: PFS and time-to-progression (TTP).

validation of the guidelines and peer-review

The minutes of the face-to-face meeting, which included the final guidelines, were validated by email by all the 31 participating experts and then submitted to a peer-review group for external comments. This group provided a formal, advisory opinion on the content and form of the initial version of the guidelines, in particular their applicability, acceptability, and readability.

discussion

In RCTs, standardized definitions of the TTE end points should be adopted to enable consistent interpretation of trial results and facilitate cross-trial comparisons and meta-analyses. Clinical trial end points often refer to efficacy, adverse events, or quality of life. In early breast cancer, effective methods of early diagnosis and new treatments have led to a longer expected survival for patients. Therefore, it is not convenient to use OS as a primary end point for many clinical trials, especially those conducted in a non-metastatic setting. Many other end points have been used to accelerate the development of news drugs and treatments, but with a lack of consistency between the different definitions used in the studies. It is therefore necessary to standardize end points to ensure the uniformity of data collection among the studies. This will make trials more useful and facilitate their implementation.

A given end point should always encompass the same set of events, as clearly highlighted by Hudis et al. [9]. However, though OS has been recognized as the least ambiguous and the most clinically relevant end point in cancer clinical trials, the other end points often used as secondary end points need to be standardized. For example, in two adjuvant clinical trials assessing the efficacy of aromatase inhibitors, the event 'second primary invasive non-breast cancer' was included for the same primary end point in the first trial [13] but not in the second [14]. This raises the possibility that a treatment could be

Table 2. DATECAN guidelines for clinical events to be included in the definitions of time-to-event end points in randomized clinical trials assessing treatments for breast cancer

Setting	Recommended Time-to-event end point	Causes of death included in definition					Clinical events included in definitions							
		From breast cancer	From non-breast cancer cause	Related to protocol treatment	From any cause	From unknown cause	Invasive ipsilateral breast tumor recurrence/ progression	Local invasive recurrence/ progression	Regional invasive recurrence/ progression (M+: regional progression)	Invasive contra lateral breast cancer	Appearance/ occurrence of metastases/ distant recurrence	Second primary invasive cancer (non-breast cancer)	Ipsilateral DCIS	Contra lateral DCIS
Non- metastatic	BCSS	X		NC										
	iDFS	X	X	X	X	X	X	X	X	X	X	X	X	X
	D-DFS	X	X	X	X	X					X			
	D-RFS	X	X	X	X	X					X			
	RFS	X	X	X	X	X	X	X	X		X		X	
	L-RFS	X	X	X	X	X	X	X	X				X	
	RFi	X					X	X	X		X		X	
	BCFi	X					X	X	X	X	X		X	X
	D-RFi	X									X			
Metastatic	PFS	X	X	X	X	X	NA	NA	X		X			
	TTP	X					NA	NA	X		X			

It was recommended not to include the following events in any of the time-to-event end points: loss to follow-up.

BCSS, breast cancer-specific survival; iDFS, invasive disease-free survival; D-DFS, distant disease-free survival; D-RFS, distant relapse-free survival; RFS, relapse-free survival; L-RFS, locoregional relapse-free survival; RFi, recurrence-free interval; BCFi, breast cancer-free interval; D-RFi, distant recurrence-free interval; PFS, progression-free survival; TTP, time-to-progression; NC, no consensus.

declared effective or inefficient depending on the definition used for the end point of the study. Birgisson et al. [15] and Nout et al. [16] showed in colorectal [15] and breast cancer [16] patients, respectively, that defining properly TTE end points is a central issue when designing trials since it may affect the estimation of treatment effect, the statistical power, and thus the final interpretation of the trial, as highlighted for respectively.

For breast cancer, Hudis et al. [9] proposed standardized definitions for many end points used in the adjuvant setting. However, these definitions of the TTE end points were based on recommendations made by an expert group in the absence of any formal international consensus method, which therefore limited their use and acceptability in current practice. Moreover, to our knowledge, no definition of TTE end points has so far been proposed for metastatic breast cancer. We thus decided to use a formal consensus methodology for the consensus process that resulted in the elaboration of standardized definitions and recommendations regarding 11 TTE end points specifically for breast cancer clinical trials. Our initial list of TTE end points was established following selected end points from published recommendations by an expert group or a literature review of recent randomized trials.

After the first round of rating, which involved 35 international experts from various medical specialties, a strong consensus was reached for only 4% of the items. After the second round of rating, the extremely low initial consensus rate went up to a strong or relative consensus for 80 events (56%). The lack of initial consensus highlighted the disparity of expert opinions and the need for harmonization despite the definitions already available for the adjuvant setting (Hudis et al. for the STEEP group) [9]. The main cause of the improvement in the consensus rates may be related to the design of the consensus process. The formal consensus process aimed to guide experts into taking position, while allowing them to maintain their opinion at each scoring round. Another reason for such an improvement may be the different rules used to define the consensus after each round: rules for the second round were slightly relaxed to ensure that the systematic exclusion of a proposal by a rater would block the consensus process [10, 11].

Moreover, the initial low consensus rate might probably also be due to misinterpretation of the text and tables. Clarification of the remaining issues at the face-to-face meeting led to a consensus for all the events except one, the 'death related to protocol treatment' event, in the definition of the end point 'BCSS'.

The consensus process also underlined some irrelevant endpoints. Indeed, during the face-to-face meeting, the experts considered DFS irrelevant in the context of breast cancer. They suggested using 'iDFS' instead of DFS, from *in situ* carcinoma that should be excluded, as recommended also by Hudis et al. One surprising result after the face-to-face meeting was the conclusion that the definitions for two different end points, D-DFS and D-RFS, should be identical. These results also questioned the relevance of some end points. The list of outcomes was based on our literature review with the objective to propose a large panel of definitions, so that researchers will find a standardized definition for the outcome that best suits the objective of their study. As D-DFS is more often used that D-RFS, in future trials, we recommend that D-DFS should be preferred to D-RFS and that a precise definition of D-RFS should be given in trials that will use this end point.

For 'invasive contralateral breast cancer' and 'second primary invasive cancer (non-breast cancer)' events, the experts adopted a conservative approach and assumed that these two events were new primary cancers unless it was proved that they were a metastasis of the studied disease. These two events were therefore not included in any end point except 'breast cancer-free interval' for invasive contralateral breast cancer and DFS (iDFS) for 'second primary invasive cancer (non-breast cancer)'.

Some recommendations were made during the face-to-face meeting. First, lost-to-follow-up should not be included in any of the previously described end points, and should be censored at the time of the status last known. Second, all deaths, whatever the cause, should be considered events for 'survival end points', except for cancer-specific survival (CSS) in which 'death from breast cancer' was proposed for inclusion. No consensus was reached for 'death related to protocol treatment', probably due to the difficulty to define precisely a death 'related to protocol treatment'. Regarding the lack of consensus for the event 'death related to protocol treatment', a recommendation was made that, in future trials, this end point should be clearly defined by referring to all the events that it includes.

One possible weakness of the consensus process is that it did not take into account rules relating to the censoring process. In this study, we have chosen to focus on recommendations about the definition of the end points and not on the recommendations about the censoring process or on the data collection procedures. When a clinical event is not included in a definition, it can be censored, ignored, or accounted for (using competing-risk analysis) in the statistical analysis, and the selected method will be study-specific depending on the objectives. Providing guidelines for events to be censored or ignored at the analysis stage is not straightforward and requires both the censoring/ignoring of events in each trial and the precise definition of the impact of the censoring process on the estimation of the treatment effect [16]. We deliberately did not address the issue related to the data collection procedures (evaluation schedules and criteria) to achieve the actual calculations of the end points defined in the manuscript with a uniform fashion. However, the measurement tools (such as the surveillance schedule, the imaging techniques, etc.) must be defined by the study while accounting for the evolution of the conceptual elements to be included in the definitions of the end points. Just like the development of standardized definitions, these issues could be addressed with consensus processes using different independent trials' scenarios (disease, setting, and treatment).

Comparison of the guidelines for the definitions of TTE end points commonly used in RCTs for breast cancer with those proposed for sarcoma/GIST and pancreatic cancers showed that similar definitions were used for all the TTE end point. For example, the three most commonly used TTE end points, such as PFS, TTP, and DFS, share exactly the same definitions across these tumor sites. Some slight differences did appear, however. First, some TTE end points can be defined for a specific cancer type. For example, disease-specific survival was proposed only for sarcoma/GIST, whereas pancreas and breast cancer guidelines defined a CSS. Similarly, time to deterioration in quality of life was defined for pancreas cancer, but not for sarcoma/GIST

and breast cancers. Second, a TTE end point can include the same events, but be named differently, e.g. 'distant metastasis-free survival' which is called 'distant-DFS' in breast cancer.

The major strength of our study lies in the formal consensus methodology used, which resulted in the elaboration of standardized definitions and recommendations regarding 11 TTE end points designed specifically for breast cancer RCT. The participation of many international experts in the consensus process increased the likelihood that these recommendations for early and metastatic breast cancer would be accepted by the scientific community, and as such contributed to their generalizability, their acceptability, and their wide-scale implementation in future research in breast cancer.

conclusion

The DATECAN initiative was set up with the objective to provide guidelines for standardized definitions of TTE end points in RCTs for different cancer sites, including pancreatic and sarcoma/GIST cancers, for which guidelines have already been finalized as well. Here, we have provided consensus definitions for the most commonly used end points in breast cancer clinical trials in both early and metastatic settings. The availability of these guidelines should improve international comparisons of trial results as well as meta-analyses. These recommendations should be disseminated for acquisition and endorsement by researchers and academic groups participating in clinical research. In addition, these guidelines should be of interest to other potential users including reviewers and editors of scientific journals, who have recently shown increased interest in the quality of the reporting of clinical trials [4, 15], regulatory authorities [5], and any research scientist body interested in improving outcome measurements and reporting of clinical trials [17]. Progress in this field also depends on the collection and publication of detailed data on the distinct clinical events that contribute to the TTE end points.

The future perspectives of the DATECAN initiative and ongoing work include extending the consensus procedure to other cancer sites (current project in stomach/esophagus, kidney, bladder, head and neck, colon, and lung cancers), assessing the impact of these definitions on academic cancer RCTs, evaluating the statistical properties of the newly defined intermediate end points (in particular PFS and DFS) as surrogates for OS, and extending the consensus to other countries (North America, India, South-east Asia, and Australia) for a worldwide view. This work is expected to provide insights into the performance of these end points to adequately capture treatment effects depending on the disease, the setting (adjuvant or metastatic), and the treatment (local, cytotoxic, or cytostatic).

acknowledgements

The authors thank Pippa McKelvie-Sebileau for medical editorial assistance, and Philip Bastable and Hélène de-Forges for editing the manuscript.

funding

This work was supported by grants from the French National League against Cancer (Ligue Nationale Contre le Cancer, 2009 National Grant for Clinical Research) and the French National Cancer Institute (Institut National du Cancer - INCa, financial support for organizing the in-person meeting held in Chicago) (no grant number).

disclosure

The authors have declared no conflicts of interest.

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